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Review article

Proposal of treatment algorithm for immune thromocytopenia in adult patients of a hematology service at a referral center in Northeastern Brazil

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ABSTRACT

Introduction: The management of adult (≥18 years) immune thrombocytopenia patients relies on platelet count, the risk of bleeding and presence of bleeding.
Objective: Confirming the diagnosis of immune thrombocytopenia and the start of therapy, our hematology service, a referral center, favors the establishment of this algorithm to treat those patients.
Results: Presentation, recently diagnosed or recurrence – group 1: life-threatening bleeding: high-dose intravenous immunoglobulins with methylprednisolone or dexamethasone. Hospitalization and platelet transfusion are considered. Group 2: Platelets $<30 \times 10^9$/L with bleeding or risk factor for bleeding, or platelets $<20 \times 10^9$/L: prednisone or dexamethasone. No response, platelets $<20 \times 10^9$/L: replace corticoid or increase doses. If platelets continue $<20 \times 10^9$/L: immunization and splenectomy. Investigation of *Helicobacter pylori*, if positive: treatment for *H. pylori*. Chronic immune thrombocytopenia with platelets $<20 \times 10^9$/L we propose two new groups (A and B): Group A: <65 years, no or low surgical risk, patient declines maintenance therapy or patient intends to get pregnant: immunization and splenectomy. Group B: failure of splenectomy (refractory) or no splenectomy indication or history of exposure to malaria or babesiosis and no response to corticoids or corticoid dependence: choose thrombopoietin receptor agonists: eltrombopag or romiplostim. Patient at high risk for arterial or venous thrombosis: recommend rituximab. After rituximab or thrombopoietin receptor agonists, if platelets continue $<20 \times 10^9$/L: indicate immunosuppressants (azathioprine or cyclophosphamide), dapsone or mycophenolate mofetil or vinca alkaloids. The goals of treatment for chronic or refractory immune thrombocytopenia are to keep platelets $>20 \times 10^9$/L and stop bleeding.

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Introduction

Immune thrombocytopenic purpura (ITP), currently called immune thrombocytopenia, is frequently observed in clinical practice. ITP is characterized by the presence of antibodies targeting platelet membrane proteins. The sensitized platelets are in turn phagocytized by the macrophages of the monocyte-macrophage system. However, the pathogenesis of ITP is complex, as it involves multiple aspects of immune deregulation and a range of different cell types (T and B lymphocytes, macrophages, dendritic cells, plasma cells), resulting in shorter platelet survival and impaired platelet production. Serum thrombopoetin levels are also reduced in ITP.[1,2] The immune nature of ITP is clear and a platelet count of 100×10^9/L was proposed as the threshold level to consider the diagnosis of ITP.[3]

The relationship between thrombocytopenia and bleeding is well documented. However, there is no clear evidence of a direct correlation between the degree of thrombocytopenia and bleeding symptoms, especially at lower platelet counts. Most ITP patients display mild to moderate thrombocytopenia which does not require treatment and for which the prognosis is good. In a large follow-up study of 292 patients treated with romiplostim by Kuter et al. (2013),[4] 51% of all bleeding events (mostly mild) occurred at platelet count levels $<50 \times 10^9$/L, 61% of severe bleeding events occurred at platelet counts $<20 \times 10^9$/L (severe thrombocytopenia) and none were considered life threatening. Overall, most bleeding events occurred with platelets $<30 \times 10^9$/L. Adults with severe thrombocytopenia also tend to experience frequent recurrences which require therapeutic intervention. Patients with severe thrombocytopenia who remain unresponsive to all forms of treatment for two years are at four times greater risk of mortality than the general population, with bleeding and infection contributing equally.[5] Schoonen et al. (2009),[6] in the United Kingdom, also showed increased mortality in ITP patients. Frederiksen et al. (2014)[7] published a twenty-year mortality in a Danish population-based cohort study of adult patients with primary ITP. The mortality rates among those patients are higher than in the general population, predominantly as a result of increased cardiovascular disease, infection, bleeding and hematological cancer, for which the cause-specific mortalities were 1.5 (95% CI: 1.1–1.5), 2.4 (95% CI: 1.0–5.7), 6.2 (95% CI: 2.8–13.5) and 5.7 (95% CI: 2.1–15.7), respectively.

Bleeding in ITP is heterogenous, unpredictable and dependent on a number of risk factors.[8,9] However, patients in excess of 30×10^9/L are at low risk for clinically important bleeding. Cortelazzo et al. (1991)[10] in a historic cohort of 117 consecutive and unselected patients with chronic ITP observed that approximately one-third of patients have platelet counts greater than 30×10^9/L at diagnosis and no significant bleeding. George and Raskob (1998)[11] believed that withholding treatment was inappropriate for patients with a platelet count less than 20×10^9/L at the time of initial diagnosis, regardless of their symptoms.

The management of such patients relies on the platelet count, risk of bleeding and presence of bleeding. Putting a stop to bleeding, complete remission (platelet count $\geq 100 \times 10^9$/L), or at least a response (platelet count $>30 \times 10^9$/L), are the goals of therapy.

Thus, in clinical practice, therapy is helpful when the platelet count is below 30×10^9/L and associated with bleeding, or below 20×10^9/L due to the high risk of bleeding, as we proposed in our treatment algorithm for adult ITP patients (Figure 1).

Objective

Based on a careful evaluation of the wide range of treatment options available for adult (≥18 years) ITP patients at our hematology service (Hospital Universitário Walter Cantídio, Federal University of Ceará), a referral center since 1982, the protocol shown in Figures 1–3 was developed. The therapeutic algorithm takes into account accumulated experience, accessibility to drugs or procedures, patient preferences and the presence of comorbidities. Special care should be taken to avoid or minimize negative impacts on quality of life secondary to adverse effects of drugs or procedures.

Before confirming the diagnosis of ITP and starting therapy, a thorough history-taking and physical examination should be conducted, including the identification of current medication, and the replacement of drugs suspected of inducing thrombocytopenia.

Due to the lack of specific laboratory tests, the diagnosis of ITP is made by ruling out other causes. This is supported by routine tests, such as peripheral blood smear, viral serology for HIV and hepatitis C virus (HVC), antiphospholipid antibodies and antinuclear antibody. A bone marrow examination is recommended for patients over 60.

Discussion

ITP has been known for centuries, but until recently no consensus had been reached on definition and treatment. In 1996, however, the American Society of Hematology published practical guidelines for diagnosis and management.[12] This was followed by recommendations on terminology, diagnosis, management and response criteria.[3,13,14] In 2011, the American Society of Hematology updated the 1996 guide.[15]

Upon initial presentation, ITP patients are classified as “acute” (diagnosed less than 3 months earlier), “persistent” (3–12 months), or “chronic” (over 12 months).[3]

In ITP patients diagnosed through routine examinations, signs and symptoms of bleeding are important indicators of when to start treatment. The purpose of therapy is not only to increase the platelet count, but also to achieve a safe level at which bleeding is unlikely or even prevented. Patients with platelet counts over 30×10^9/L, and without bleeding, require no treatment and may be followed periodically, since the risk of clinically significant bleeding is very low. In our algorithm (Figure 1), we propose treating patients with platelet counts below 30×10^9/L, associated with bleeding, or below 20×10^9/L due to the high risk of bleeding.

The high risk of bleeding is defined as: age over 60 years, uncontrolled hypertension, use of drugs (anticoagulants, antiaggregants, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapy, peptic ulcer or inflammatory bowel disease,

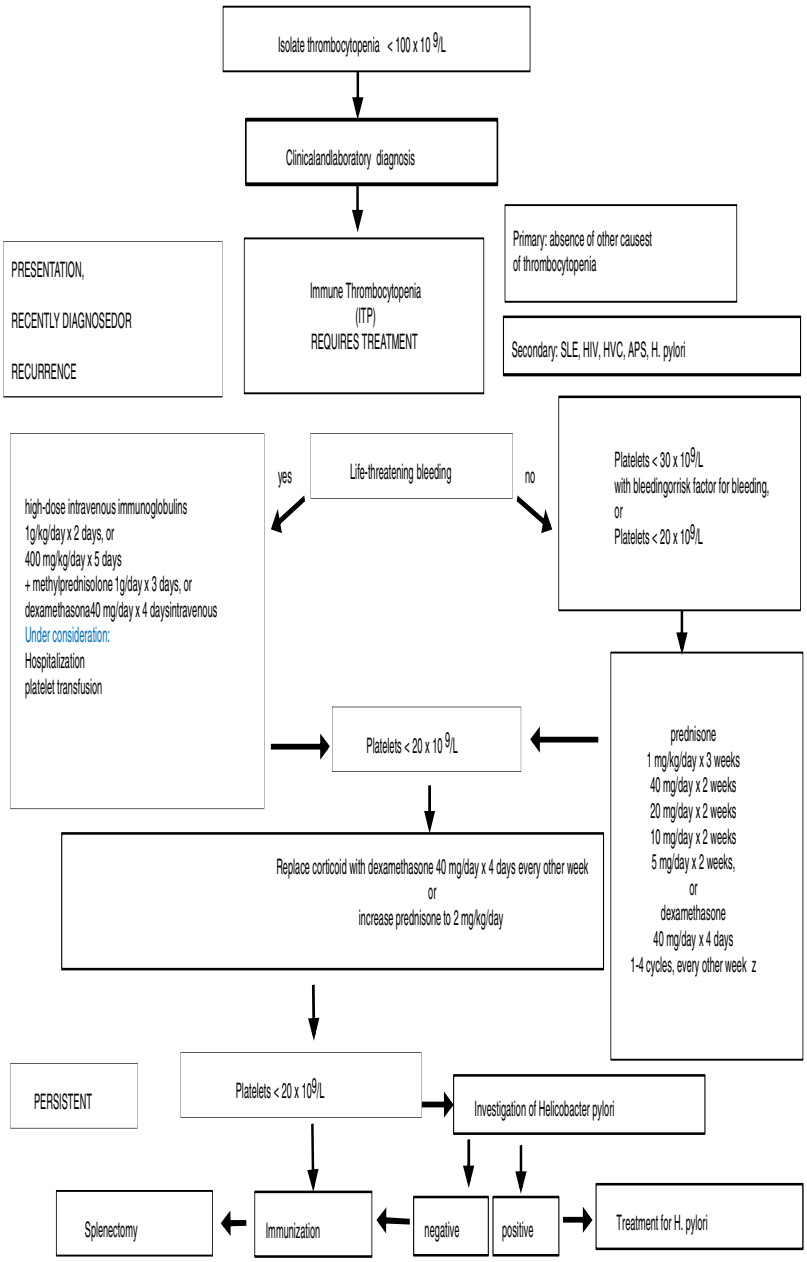

Figure 1 – Treatment algorithm for adult patients with immune thrombocytopenic purpura (ITP) attending a referral center in Northeastern Brazil – recently diagnosed or recurrence/persistent ITP. Systemic lupus erythematosus (SLE), HIV, hepatitis C virus (HVC), antiphospholipid syndrome (APS), *Helicobacter pylori* (*H. pylori*).

cirrhosis, uremia, congenital hemorrhagic disease, history of bleeding, trauma, surgery, delivery, and occupational or recreational activities with a high risk of bleeding. According to Cohen et al. (2000),[16] the expected mortality in 5 years was 47.8% for patients over 60, compared to 2.2% for patients under 40. The presence of extensive purpura or hemorrhagic bullae in the mucosa may be considered life-threatening bleeding.

Life-threatening bleeding may occur in association with trauma, bleeding from the central nervous system or gastrointestinal tract, massive hematuria or internal hematoma, when the patient is in need of surgery or in labor. Fortunately, severe or life-threatening bleeding is not common (adults: 9.6%).[9] In a bleeding emergency, hospitalization with high-dose intravenous immunoglobulin therapy is recommended: 1 g/kg/day for two days or 400 mg/kg/day for five days, associated with corticoids: methylprednisolone 1 g/day for three days or high doses of prednisone or dexamethasone.[11,14,15] The effect of high doses of intravenous immunoglobulins may involve blocking of the Fc receptors of the macrophages. High-dose methylprednisolone therapy achieves 80% response.[15] In most patients, this increases the platelet count faster (2–3 days after infusion) than therapy with oral corticoids, but high doses of immunoglobulins may produce adverse effects upon

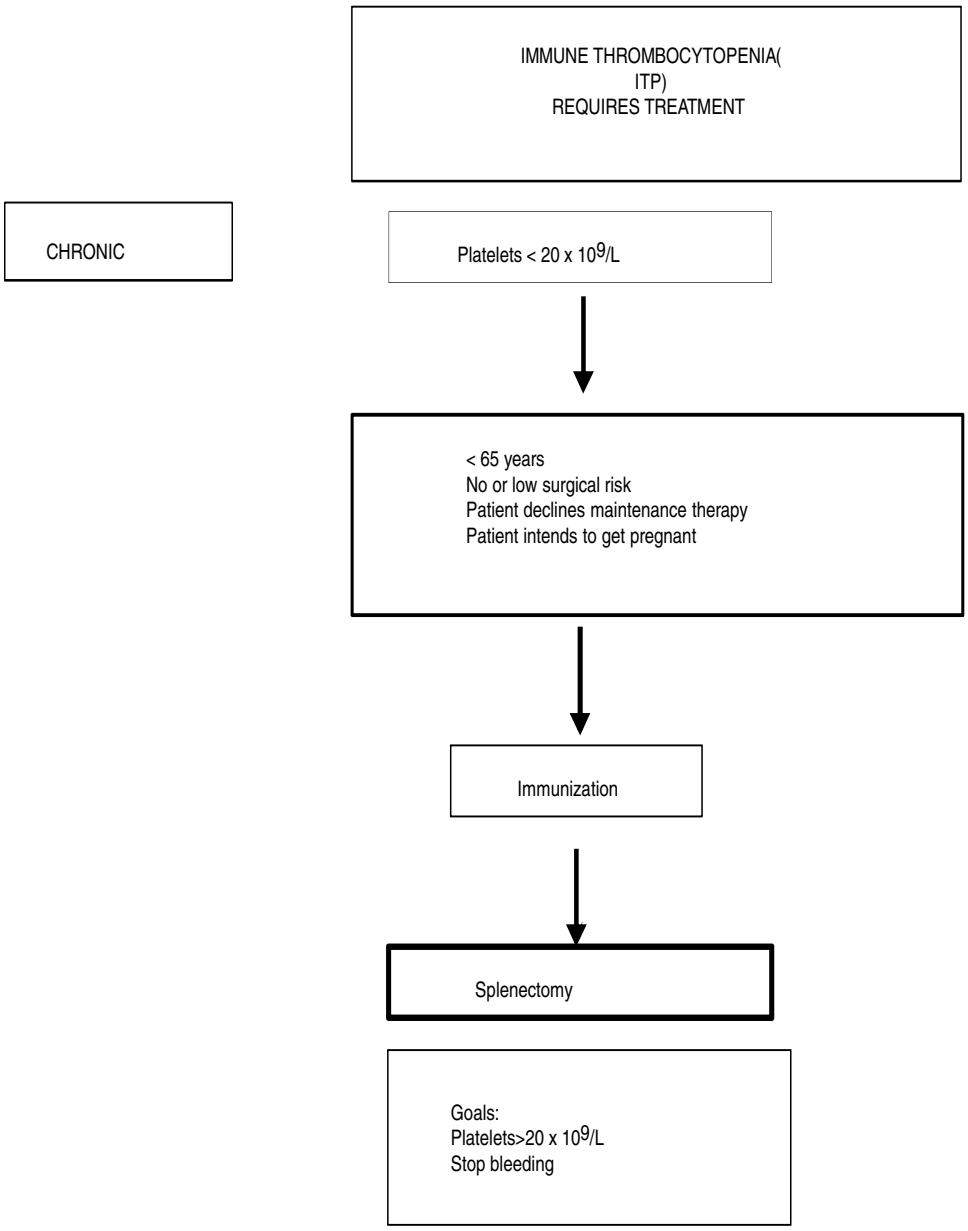

Figure 2 – Treatment algorithm for adult patients with immune thrombocytopenic purpura (ITP) attending a referral center in Northeastern Brazil – Chronic ITP.

infusion, in addition to the risk of headache, aseptic meningitis and thrombosis.

Platelet transfusion is important when treating life-threatening bleeding. Though rapidly destroyed, the platelets help form clots at bleeding sites, improving hemostasis. Transfusion is more effective if performed after infusion of high-dose intravenous immunoglobulins because the immunoglobulins increase platelet survival.[17] The concomitant infusion of high-dose intravenous immunoglobulins and platelets appears to be effective at quickly raising the number of platelets in situations of life-threatening bleeding and imminent surgery.[18] Antifibrinolytics may be used to further reduce bleeding but should be avoided in cases of hematuria due to the risk of thrombi in the glomeruli, renal pelvis and ureters. According to our algorithm, high-dose intravenous immunoglobulins with intravenous methylprednisolone or dexamethasone are proposed in life-threatening bleeding. Hospitalization and platelet transfusion may be considered (Figure 1).

Considered first-line initial treatment (unless contraindicated), corticoids (i.e., prednisone and dexamethasone) increase the platelet count through several mechanisms, such as inhibition of phagocytosis by macrophages, reduction in antibody production, and increased platelet production.[14,19,20] They also seem to reduce capillary permeability, thereby limiting blood loss. However, corticoids can have serious adverse effects, such as hyperglycemia, hypertension, gastritis, cataract, osteoporosis, aseptic bone necrosis, opportunistic infections and behavior change.[14] Prednisone is more commonly used than dexamethasone.[14,15] Response to

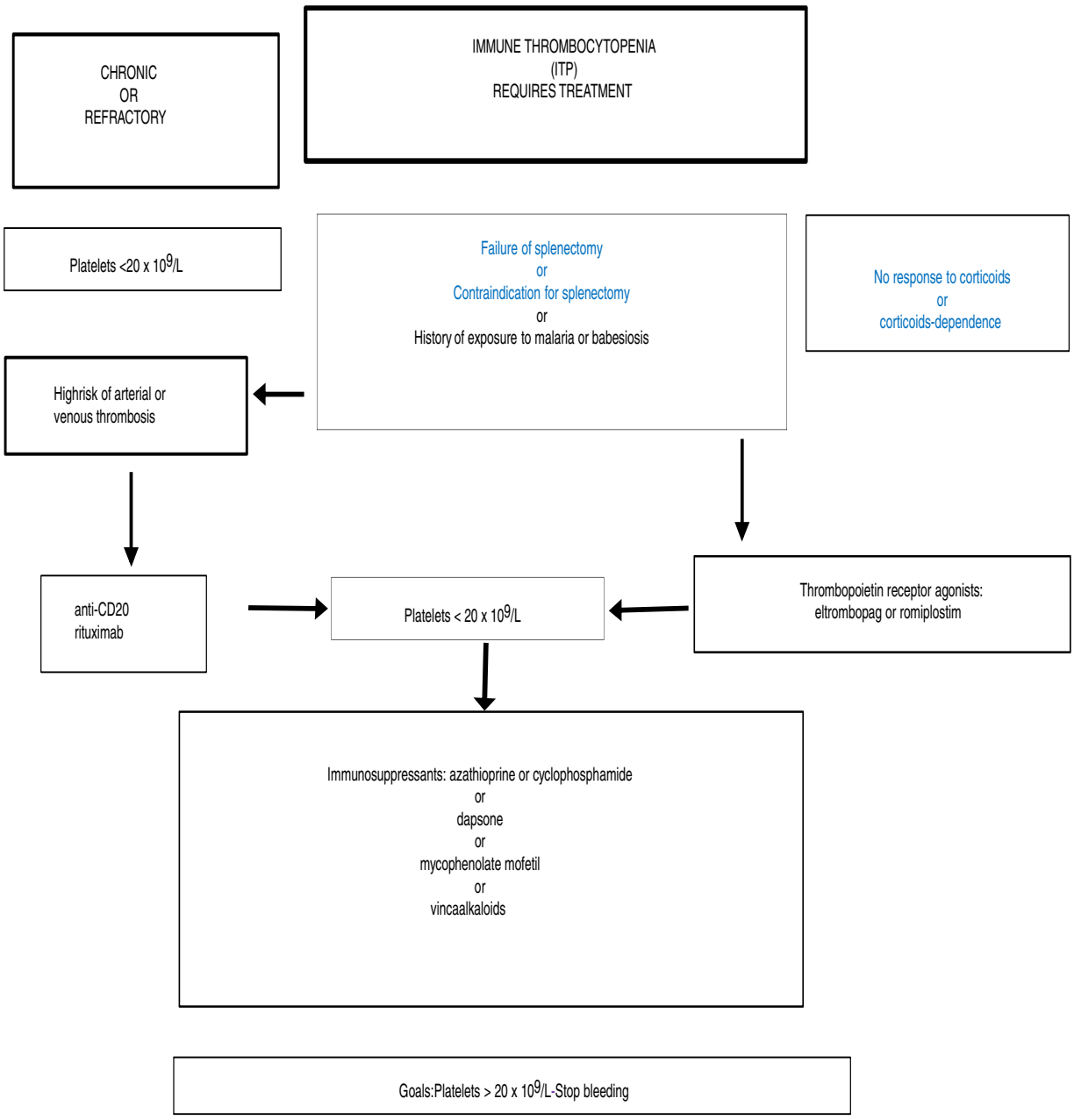

Figure 3 – Treatment algorithm for adult patients with immune thrombocytopenic purpura (ITP) attending a referral center in Northeastern Brazil – Chronic or Refractory ITP.

prednisone (1–2 mg/kg/day) occurs in three weeks, but two-thirds of patients achieve a platelet count above 50×10^9/L in one week. When the dose is reduced, some patients experience recurrence of thrombocytopenia, resulting in low remission rates in the long term.[14]

There is no consensus regarding the duration of initial therapy,[21] but therapy should continue until a safe number of platelets is reached. If the patient is responsive, prednisone (1 mg/kg/day) should be maintained for three weeks before weaning is attempted. Sustained response varies from 5 to 50%. As for dexamethasone, the rationale is to provide therapy with an equivalent amount of corticoid, but with a shorter exposure time. The standard dose is 40 mg/day for four days, in one or four cycles, repeated every other week (resulting in a response rate of 89.2% in recently diagnosed patients) or 40 mg/day for four days, repeated once a month, depending on the platelet count.[22] At six months, overall response and platelet count are the same for dexamethasone and prednisone. High doses of dexamethasone are preferred when a rapid increase in platelets is desired.[23] Thus, the choice of drug should contemplate the patient profile, possible adverse effects, long-term compliance, and need for rapid response (such as provided by dexamethasone). Despite the favorable response obtained with all these drugs, the American Society of Hematology (2011) still recommends prednisone 1–2 mg/kg/day as first-line treatment for ITP.[15] In

our algorithm, we also propose prednisone as the first drug. If there is no response, dexamethasone is the second-line drug (Figure 1). If the patient does not respond to corticoids in three weeks, alternatives should be considered.

Second-line treatment options include splenectomy, immunosuppressants, immunomodulators, cytotoxic agents and thrombopoietin receptor agonists.

Splenectomy is indicated for patients refractory to corticoids (i.e., with platelet counts under 20×10^9/L). Depending on the clinical condition, splenectomy is deferred in most patients for at least 6 months. This may be due to patient preference or other active comorbidities, as well as to the understanding that spontaneous improvement or late remission may occur 6–12 months after diagnosis, according to the International Consensus Statement.[14] Deferral of the splenectomy until the chronic phase (12 months) was suggested if possible, unless an adequate count cannot be maintained with medical therapy, adverse reactions to medical alternatives develop, or there is a compelling patient preference (e.g., lifestyle or employment).[24] In a systematic review, Mikhael et al. (2009)[25] observe that six studies reported a duration of ITP at the time of surgery which averaged 26.1 months (range: 0–420 months). Emergency splenectomy has been also reported to be successful in refractory ITP with bleeding, but reports of its use in this situation are rare. The major indication for emergency splenectomy in these seven patients was based on the warning signs of intracranial hemorrhage (six of seven patients). The interval between the initial symptoms of ITP and emergency splenectomy varied from six days to five months.[26]

Splenectomy is associated with an initial response (platelets $>100 \times 10^9$/L) of 65–70% and, among those who respond, 60–70% maintain a normal platelet count for years. Around 50% of ITP patients can be cured with a splenectomy.[27] In a retrospective analysis, Vianelli et al. (2013)[28] confirmed these results: of 233 patients at six European institutions undergoing splenectomy between 1959 and 2001, and followed for at least 10 years postoperatively, 180 (77%) had complete response and 26 (11%) had partial response. Sixty-eight (33%) of these 206 responders experienced recurrence, usually within four years of the first response. Moreover, in 138 patients (59%), response was maintained without therapy. It should be kept in mind that candidates for splenectomy must be immunized against the Haemophilus influenza type B, polyvalent pneumococcal and quadrivalent meningococcal polysaccharide, and potential risks (infection, thrombosis, pulmonary hypertension and immediate postoperative complications) should be discussed with them.[29] A study involving physicians from Oklahoma showed that experienced hematologists-oncologists were more likely to choose splenectomy as second-line treatment.[30] Thus, splenectomy remains the standard second-line option, although rituximab tends to achieve similar results.[2,27] In our service, if the platelet count is still under 20×10^9/L, we propose splenectomy in persistent and chronic ITP (Figures 1 and 2). Splenectomy is indicated for patients <65 years with no or low surgical risk or for those who decline maintenance therapy or intend to get pregnant.

After 2001, the management of ITP has changed with the advent of drugs such as rituximab (anti-CD20 antibody) and thrombopoietin receptor agonists. These drugs are proposed in our algorithm if the platelet count is still $<20 \times 10^9$/L, and always when there is corticoid dependence or no response to corticoids in chronic or refractory ITP. The former is defined by persistence of severe ITP after splenectomy (Figure 3).

The B-lymphoid cells play an important role in immune response and may lead to the development of autoimmune disorders (especially ITP) through the production of platelet-bound antibodies. By depleting peripheral B-lymphoid cells, rituximab is helpful in the treatment of lymphoma and autoimmune disorders, such as ITP.[31] In one study, the overall initial response rate of rituximab was 57%, while 21% of responders maintained treatment-free response for at least 5 years without significant toxicity.[32] Rituximab also had an influence on the different T-cell subsets, including restoration of the Th1/Th2 balance and elevation of immune regulatory T cells (Tregs), which suppress cell-mediated and antibody-mediated responses and protect the host against autoimmunity.[2,33,34] The combination of rituximab and corticoids improves immunomodulation and the effect is more persistent[35] and platelet counts $>50 \times 10^9$/L are sustained longer than when the corticoid is used alone. However, the association of these two drugs is rarely regarded as standard treatment. Before prescribing rituximab, the following should be taken into account: (I) after rituximab, response to vaccines may be compromised; (II) if splenectomy becomes necessary, the impact tends to be greater; (III) the relative cost is high, and; (IV) rituximab produces significant adverse effects.[22] Rituximab, in our algorithm, will be proposed for chronic ITP patients if the platelet count is still $<20 \times 10^9$/L after failure of splenectomy or contraindication for splenectomy or history of exposure to malaria or babesiosis. Rituximab will always be considered for patients at high risk of arterial or venous thrombosis (Figure 3), since thrombopoietin receptor agonists have been associated with thromboembolic events.

The observation of impaired platelet production in ITP led to the development of agents capable of binding to the thrombopoietin receptor and stimulating thrombopoiesis.[36,37] Approved by the "US Food and Drug Administration" (FDA) in 2008, the thrombopoietin receptor agonists romiplostim and eltrombopag achieve responses of 80% and 90%, respectively. Some authors claim that a small number of patients experience an increase in platelet count and remission.[38,39] In Europe, their use is restricted to patients with ITP refractory to splenectomy or contraindication for surgery. However, thrombopoietin receptor agonists are being used in patients with persistent ITP before splenectomy or refractory to first-line therapy. Unfortunately, to date no study with a long-term follow-up has compared romiplostim and eltrombopag. The adverse effects of thrombopoietin receptor agonists include thrombosis, thrombocytosis, transaminitis, eltrombopag-related cataract and changes in the reticular network of the bone marrow.[15,27] These treatments have been shown to be efficacious, though costly.[22] According to a clinical protocol and treatment guideline published by the Brazilian Ministry of Health in November 2013,[40] romiplostim is currently used only in clinical trials. The same publication identifies eltrombopag as potentially useful in the treatment of chronic ITP, but the compound needs to be proven efficacious, effective and safe in clinical trials before being

considered a feasible alternative. Kuter et al. (2013)[4] demonstrated that romiplostim was safe and well-tolerated over 614 patient-years of exposure in ITP patients, and that efficacy was maintained with stable dosing for up to 5 years of continuous treatment. A platelet response was achieved at least once by 95% of patients, with a platelet response maintained by all patients on a median 92% of study visits. Treatment-related serious adverse events were infrequent and did not increase with longer treatment. In an open-label EXTEND study on 302 chronic/persistent ITP patients, Wong et al. (2017)[41] concluded that long-term use of eltrombopag (mean 2.37 years; range 2 days to 8.76 years) was efficient in maintaining a platelet count above 50×10^9/L, and reduced bleeding for over 6 months in most patients, with few significant adverse effects (thrombosis, hepatobiliary events and marrow fibrosis).

Audia et al. (2016)[42] raised the question of whether "older drugs" with low cost and a well-documented risk/benefit profile could be employed in the treatment of ITP. With a response rate of 30–50%, dapsone is an interesting second-line option for use immediately after corticosteroids. When used at a dose of 75–100 mg/day, partial and complete remission rates are approximately 50% and 20%, respectively, but platelet counts return to baseline levels after discontinuation of the therapy.[43,44] The mechanism of dapsone action in ITP is not known. The most important side effects are nausea, headache, skin rashes, hepatitis, cholestasis, dose-dependent hemolysis, and methemoglobinemia. Dapsone should not be given to patients with glucose-6-phosphate dehydrogenase deficiency. The efficacy of dapsone is reached after 3–6 weeks. Hydroxychloroquine is associated with a 50% response rate in patients positive for antinuclear antibodies. Danazol is preferably used in older patients due to its virilizing effects and risk of liver cancer. To get the most benefit with danazol, follow-up with transaminases is recommended, and prostate cancer and history of thrombosis should be ruled out. Vinca alkaloids (vimblastina is less toxic than vincristine) may be used temporarily in patients refractory to high-dose intravenous immunoglobulins, and represent an alternative before surgery, especially splenectomy, because they transiently increase the platelet count in approximately 70% of ITP patients within 5–21 days, but produce sustained remissions in only 10% of treated patients. The recommended dose of vincristine is 1–2 mg, and of vinblastine, 0.1 mg/kg (maximum: 10 mg), at 1-week intervals for a minimum of three courses. Peripheral neuropathy, neutropenia, jaw pain, alopecia, and constipation are complications of treatment with vinca alkaloids.[45] In the HEMORIO (2014) protocol for ITP,[46] cyclophosphamide (1–2 mg/kg/day for 16 weeks) and azathioprine (1–2 mg/kg/day, max 150 mg/day) are indicated as second-line treatment for persistent or chronic thrombocytopenia unresponsive to rituximab or splenectomy, with a response rate of 24–85% for the former and 40% for the latter, although up to six months may be required to achieve response with azathioprine. Azathioprine works by suppressing the immune response. One study reported that azathioprine produced a sustained normalization of the platelet counts in up to 45 percent of patients with refractory ITP.[47] *Cyclophosphamide* increases platelet counts in 60–80% of patients with ITP, and 20–40% of those patients will remain in remission for 2–3 years after receiving 2–3 months of therapy. *Cyclophosphamide* and azathioprine are immunosuppressive drugs and the major adverse effects are marrow suppression and possible increased risk of secondary malignancy. Immunosuppressive drugs are indicated in patients older than 60 years old. Using mycophenolate mofetil (500 mg twice a day, raised to 1 g twice a day when tolerated), Cooper (2017)[48] observed late response (6–8 weeks) and, in some patients, treatment could be discontinued after some years because complete response was achieved for over 12 months. The adverse effects included headache, gastrointestinal toxicity, abnormal liver function and increased infections. According to Cuker and Neunert (2016),[45] these immunosuppressants should only be used after corticoids, rituximab and thrombopoietin receptor agonists. We agree with Cuker and Neunert, as shown in Figure 3. When indicated, an immunosuppressant should be combined with corticoids, rituximab and thrombopoietin receptor agonists or other immunosuppressants with different mechanisms.[49]

In addition to pharmacological management, the American Society of Hematology (2011) suggests screening ITP patients for *Helicobacter pylori*. If positive, the infection should be eradicated.[15] The discovery by Gasbarrini et al.[50] in 1998 that the platelet count increases after eradication of *H. pylori* infection spurred much research worldwide, but with highly inconsistent results (0–100%). A recent study conducted at our Hematology service on chronic ITP patients showed that 4 (30%) of 13 patients with successful eradication of *H. pylori* experienced an increase in platelet count which was maintained during 12 months of follow-up.[51] The authors pointed out that the platelet response was not associated with previous platelet counts, duration of chronic ITP, sex, age, previous use of medication or splenectomy.[51] Emilia et al. (2007)[52] and Tsumoto et al. (2009)[53] conducted studies on chronic ITP patients with long follow-up and found that in those who responded to treatment for *H. pylori* the increased number of platelets was maintained with no need for further treatment of ITP for over 12 months. Barbosa et al. (2017)[51] reported similar results and concluded that treatment for ITP may be discontinued without negative impacts in this patient population. In our algorithm, we propose *H. pylori* screening in persistent ITP patients. If positive, treatment is indicated (Figure 1).

Conclusion

The lack of a predictor of response to treatment for ITP, regardless of the drug or procedure (splenectomy), favors the establishment of an algorithm for therapy for this pathology.

Perspectives

Medical management of ITP should be up-to-date with advances in treatment, including new compounds, benefits and adverse effects of drugs and long-term studies on medication for ITP. The growing understanding of the pathogenesis of ITP is encouraging researchers to explore new combinations of drugs.

Conflicts of interest

The authors declare no conflicts of interest.

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